

What is claimed is:

- Sub
a14
- 5
1. A method for treating a gastrointestinal disorder in a mammal suffering from or susceptible to the disorder, the method comprising administering to the mammal a therapeutically effective amount of a compound that increases nitric oxide (NO) activity as measured in a standard gastric emptying assay.
 2. A method for treating a gastrointestinal disorder in a mammal suffering from or susceptible to the disorder, the method comprising administering to the mammal a therapeutically effective amount of at least one compound that provides increased nitric oxide synthase (nNOS) as measured in a standard nNOS protein expression assay.
 - 10
 3. The method of claim 1 or 2 wherein the mammal has been identified and selected for treatment to increase at least one of the NO activity and the nNOS level, and the compound is then administered to the identified and selected mammal.
 - 15
 4. The method of any one of claims 1 through 3 wherein the amount of the administered compound is sufficient to increase neuronal cyclic guanosine 3'-monophosphate (cGMP) levels as measured by a standard cGMP assay.
 - 20
 5. The method of any one of claims 1 through 4 wherein the gastrointestinal disorder is characterized by hypomotility or hypermotility in at least one of the small intestine, large intestine, colon, esophagus or stomach.
 - 25
 6. The method of any one of claims 1 through 5 wherein the gastrointestinal disorder is further characterized by at least one of nausea, vomiting, heartburn, postprandial discomfort, diarrhea, constipation, and indigestion.
 - 30
 7. The method of any one of claims 1 through 6 wherein the disorder is associated with at least one of diabetes, anorexia nervosa, bulimia, achlorhydria, achalasia, anal fissure, irritable bowel syndrome, intestinal pseudoobstruction, scleroderma and gastrointestinal damage.

8. The method of claim 7 wherein the disorder is diabetic gastropathy.

5 9. The method of claim 7 wherein the intestinal pseudoobstruction is at least one of colonic pseudoobstruction (Ogilvie's syndrome), idiopathic gastroparesis, and idiopathic constipation (megacolon).

10 10. The method of claim 7 wherein the gastrointestinal damage is a consequence of surgical intervention.

11. The method of claims 1-9, wherein the gastrointestinal disorder is at least one of hypertrophic pyloric stenosis, functional bowel disorder, gastroesophageal reflux disease (GERD), Barrett's metaplasia or Barrett's esophagus.

15 12. The method of claim 10 wherein the functional bowel disorder is at least one of irritable bowel syndrome or functional dyspepsia.

20 13. The method of any one of claims 1 through 4 wherein the mammal is suffering from or susceptible to Crohn's disease or ulcerative colitis.

25 14. The method of any one of claims 1 through 14 wherein a PDE inhibitor compound is administered.

15. The method of any one of claims 1 through 14 wherein insulin, a biologically active variant of insulin, or a compound that boosts insulin effects or levels.

30 16. The method of claim 15 wherein the compound that boosts insulin effects or levels is a sulfonylurea or a thiazolidinedione.

17. A method for treating a gastrointestinal disorder in a mammal suffering from or susceptible to the disorder, comprising administering to the mammal a therapeutically effective amount of a phosphodiesterase (PDE) inhibitor in an amount

sufficient to augment nitric oxide (NO) production as measured in a gastric emptying assay.

Sub A13

5 18. A method for treating a gastrointestinal disorder in a mammal suffering from or susceptible to the disorder, comprising administering to the mammal a therapeutically effective amount of insulin, a biologically active variant thereof, or other compound that can boost insulin effects or levels in an amount sufficient to provide increased nitric oxide synthase (nNOS) levels as measured in a standard nNOS protein expression assay.

10 19. The method of claim 17 wherein the PDE inhibitor decreases activity of a cyclic guanosine monophosphate (cGMP) specific PDE as determined by at least one of a standard PDE or PDE5 assay.

Sub A3

15 20. The method of claims 17 or 19 wherein the inhibitor decreases activity of a type 5 PDE (PDE5).

20 21. The method of claims 17, 19 or 20 wherein the PDE inhibitor has an IC_{50} of about 0.5 mM or less in the standard PDE or PDE5 assay.

25 22. The method of any one of claims 17 or 19 through 21 wherein the amount of the administered PDE inhibitor is further sufficient to increase neuronal cyclic guanosine 3'-monophosphate (cGMP) as measured by a standard cGMP assay.

25 23. The method of claim 18 wherein the compound that boosts insulin effects or levels is a sulfonylurea or a thiazolidinedione.

Sub A4

30 24. The method of claim 18 or 23 wherein the compound that can boost insulin effects or levels is administered in conjunction with a PDE inhibitor compound.

25. The method of any one of claims 1 through 24 wherein at least one of the administered compounds is represented by anyone of Formulae I through XIII as those

Sub
A4

formulae are set forth above as well as pharmaceutically acceptable salts and solvates thereof.

26. The method of claim 25 wherein the administered compound is at least one of a pyrazolo[4,3-d] pyrimidin-7-one, a pyrazolo[3,4-d] pyrimidin-4-one, a quinazolin-4-one, a purin-6-one, or a pyrido[3,2-d]pyrimidin-4-one, or a pharmaceutically acceptable salt thereof.

27. The method of claim 25 wherein the administered compound is at least one of the following compounds as represented above by one or more of Formulae I-V as those formulae are set forth above:

28. The method of claim 25 wherein the administered compound is one or more of:

5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil),

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-[5-(2-morpholinocarbonyl-ethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,
 2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one,
 2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one,
 8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one,
 8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one,
 8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one,
 2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,
 2-[5-(4-carboxypiperidinosulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,
 2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,
 2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one; or a pharmaceutically acceptable salt thereof.

29. The method of any one of claims 1 through 28 wherein Viagra is administered to the mammal.

30. The method of any one of claims 1-29 wherein the administered compound increases nNOS in the gastrointestinal neurons or interstitial cells of Cajal by at least about 10% as determined by the standard nNOS protein expression assay.

31. The method of any one of claims 1 through 30 wherein the administered compound increases nNOS in the gastrointestinal neurons or interstitial cells of Cajal by between from about 15% to about 50% as determined by the standard nNOS protein expression assay.

32. The method of any one of claims 1 through 31 wherein the compound increases cGMP by at least about 10% as determined by the cGMP assay.

5 33. The method of any one of claims 1 through 32 wherein the administered compound decreases PDE5 activity by at least about 10% as determined by at least one of the standard PDE or PDE5 activity assay.

10 34. The method of any one of claims 1 through 33 wherein the administered compound decreases PDE5 activity by between from about 20% to about 50% as determined by at least one of the standard PDE or PDE5 activity assay.

15 *Sub 13* 35. A method for preventing or treating a diabetic gastropathy in a mammal comprising administering to the mammal a therapeutic amount of one or more of the compounds represented above by Formulae I through XIII as those formulae are set forth above, or a pharmaceutically acceptable salt thereof.

20 36. The method of claim 35 wherein the administered compound is at least one of the compounds represented by Formulae I-V as those formulae are set forth above or a pharmaceutically acceptable salt thereof.

25 37. The method of claim 35 wherein the administered compound is at least one of a pyrazolo[4,3-d] pyrimidin-7-one, a pyrazolo[3,4-d] pyrimidin-4-one, a quinazolin-4-one, a purin-6-one, or a pyrido[3,2-d]pyrimidin-4-one or a pharmaceutically acceptable salt thereof.

38. The method of claim 35 wherein the administered compound is at least one of the following compounds:

30 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3d]pyrimidin-7-one (sildenafil),

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7 H-pyrazolo[4,3-d]pyrimidin-7-one,

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one,

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5 6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

10 6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

15 3-methyl-6-[5-(2-morpholinocarbonyl-ethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4(3H)-one,

20 2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one,

8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one,

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one,

25 8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one,

2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

2-[5-(4-carboxypiperidinosulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

30 2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one; or a pharmaceutically acceptable salt thereof.

5 39. The method of claim 35 wherein the administered compound is Viagra.

40. The method of any one of claims 35 through 39 wherein insulin, a biologically active variant of insulin, or a compound that can boost insulin effects or levels is administered to the mammal.

10

41. The method of claim 40 wherein the compound that boosts insulin effects or levels is a sulfonylurea or a thiazolidinedione.

15

Sub A13
42. A method for preventing or treating a diabetic gastropathy in a mammal comprising administering to the mammal a therapeutic amount one or more of insulin or a biologically active variant thereof, or a compound that can boost insulin effects or levels in the mammal.

20

Sub A6
43. The method of any one of claims 35 through 42 wherein the mammal has been identified as suffering from diabetic gastropathy and selected for treatment for diabetic gastropathy.

25

Sub A13
44. A method for treating a mammal suffering or susceptible to diabetes, anorexia nervosa, bulimia, achlorhydria, achalasia, anal fissure, irritable bowel syndrome, intestinal pseudoobstruction, scleroderma, gastrointestinal damage, Crohn's disease or ulcerative colitis, comprising administering to the mammal an effective amount of one or more of the compounds represented above by Formulae I through XIII as those formulae are set forth above, or a pharmaceutically acceptable salt thereof.

30

45. The method of claim 44 wherein the administered compound is at least one of the compounds represented by Formulae I-V as those formulae are set forth above or a pharmaceutically acceptable salt thereof.

46. The method of claim 44 wherein the administered compound is at least one of a pyrazolo[4,3-d] pyrimidin-7-one, a pyrazolo[3,4-d] pyrimidin-4-one, a quinazolin-4-one, a purin-6-one, or a pyrido[3,2-d]pyrimidin-4-one or a pharmaceutically acceptable salt thereof.

47. The method of claim 44 wherein the administered compound is at least one of the following compounds:

5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil),

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-(5-morpholinomethylsulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

6-[5-(2-tert-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

3-methyl-6-[5-(2-morpholinocarbonyl-ethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4(3H)-one,

2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one,

8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one,

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one,

5 8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one,

2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

2-[5-(4-carboxypiperidin-sulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

10 2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one,

2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one; or a pharmaceutically acceptable salt thereof.

15

48. The method of claim 44 wherein the administered compound is Viagra.

Sub
A7
20 49. The method of any one of claims 44 through 48 wherein insulin, a biologically active variant of insulin, or a compound that boosts insulin effects or levels is administered to the mammal.

50. The method of claim 49 wherein the compound that boosts insulin effects or levels is a sulfonylurea or a thiazolidinedione.

Sub
A8
25 51. The method of any one of claims 44 through 50 wherein the mammal has been identified as suffering from diabetes, anorexia nervosa, bulimia, achlorhydria, achalasia, anal fissure, irritable bowel syndrome, intestinal pseudoobstruction, scleroderma, gastrointestinal damage, Crohn's disease or ulcerative colitis, and the mammal has been selected for treatment for diabetes, anorexia nervosa, bulimia, achlorhydria, achalasia, anal fissure, irritable bowel syndrome, intestinal
30 pseudoobstruction, scleroderma, gastrointestinal damage, Crohn's disease or ulcerative colitis.

52. The method of any one of ~~claims~~ 1 through 51 wherein the mammal is primate, rodent, rabbit or a domesticated animal.

5 53. The method of any one of ~~claims~~ 52 wherein the mammal is a human patient.

54. The method of any one of claims 1 through 53 wherein the mammal has been subjected to or will be subjected to treatment with at least one prokinetic agent.

10 55. The method of any one of claims 1 through 54 wherein the method further comprises administering to the mammal a therapeutically effective amount of at least one prokinetic agent.

15 ~~Sub A9~~ ~~56~~ 57. The method of claim 54 or 55 wherein the prokinetic agent is metoclopramide, domperidone, erythromycin or cisapride.